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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

EPPERSON, JON D

ART UNIT

PAPER NUMBER

1627

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary*File Copy*

Application No.

09/783,083

Applicant(s)

DUKLER ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The priority filing date of 2/17/1999 is acknowledged. No claims were amended, added, or cancelled. Therefore, claims 30-58 are pending and under examination.

Response to Restriction and Election of Species without Traverse

2. Applicant's species election on July 2, 2002 without traverse in Paper No. 5 is acknowledged.

3. Please note: Applicant's elected species for subgroups 1-5, 7-8 were found in the art, see rejections below. Applicant is reminded of MPEP § 803.02 with respect to species elections:

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

4. Please note: Applicant's elected species for subgroup 6 was not found in the art.

Applicant is reminded of MPEP § 803.02 with respect to species elections (cited in part):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in

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response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Applicant's claims were first searched to the extent of the elected species. No art was found, thus the search was extended. The art search was extended to all species and no prior art was found that anticipates or renders obvious the instant claims based solely on the species election of subgroup 6. However, the rejections below apply to the claims.

5. No claims were withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

6. Therefore, claims 30-58 are examined on the merits in this action to the extent of the species election described above.

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

Abstract

8. The abstract is too short and does not fully describe the claimed invention. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

- (1) if a machine or apparatus, its organization and operation;
- (2) if an article, its method of making;
- (3) if a chemical compound, its identity and use;
- (4) if a mixture, its ingredients;
- (5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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10. Claims 30-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the limited number of complex carbohydrate libraries disclosed, does not reasonably provide enablement for *any* complex carbohydrate library, which claim 1 literally encompasses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of claim 1 encompasses complex carbohydrate libraries with carbohydrate members that are unbounded by the number of saccharide subunits, substituents or the degree and type of linkages between saccharide units or saccharide units and other substituents. Furthermore, claim 1 encompasses complex carbohydrate libraries, which contain carbohydrate members that have yet to be prepared or envisioned. Furthermore, claim 1 encompasses complex carbohydrate libraries, which contain unusual or unnatural sugars as substrates, which may not be good substrates for the enzymes disclosed by applicant. Consequently, the examples set forth in the specification do not constitute support for the entire scope of claim 1 and, as a result, the entire scope of claim 1 could not be supported without undue experimentation.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;

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- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Claim 1 is drawn to a method comprising the steps of “producing an addressable combinatorial complex carbohydrate library.” Such a claim represents a broad scope because it reads on all possible complex carbohydrates (even ones that have yet to be synthesized) including complex carbohydrate libraries that contain unusual or unnatural sugars, which may not be good substrates for the enzymes disclosed by applicant.

(3 and 5) The state of the prior art and the level of predictability in the art:

According to the applicants, “[a]lthough carbohydrate libraries of limited complexity have been synthesized using various chemical methods, a combinatorial library of complex carbohydrates with a high rank of structural complexity resembling natural complex carbohydrates (e.g., highly branched structures) has not yet been produced” (see page 10 of specification, lines 11-15). The applicants further state that “the unavailability of an efficient and comprehensive synthesis method applicable for producing diverse and complex carbohydrate species” has led to a lag in discovering new carbohydrate-derived pharmaceutical reagents (see page 14 of specification, lines 16-20). Consequently, the state of the prior art does not provide adequate guidance for one of skill in the art to predict how to synthesize *any* complex combinatorial carbohydrate library (especially those libraries not disclosed by the applicants) without undue experimentation especially libraries that contain unusual or unnatural sugars.

Furthermore, the use of enzymes in synthetic reactions are inherently “unpredictable” because unpredictable steric effects often prevent the desired enzymatic reaction. For example, applicant verified the β -1,4-galactosyltransferase mediated addition of β -D-galactose to “the plate immobilized phenyl- β -D-GlcNAc” using a 22 atom linker, but was not able to detect any transfer of β -D-galactose to “the plate immobilized β -D-GlcNAc” using a 20 atom linker. The applicant “suggested” that the differences in reactivity were caused by the small change in “linker length” i.e., 22 to 20 atoms, which clearly demonstrates the “unpredictable” nature of these enzymatic reactions (see page 81, lines 13-19). Furthermore, applicant acknowledges this limitation and others by stating that the “linker length, flexibility of the complex carbohydrate, immobilization of carbohydrate groups and steric hinderance are also important factors effecting synthesis efficiency” (see page 87, lines 4-6).

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability (see above), would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have only provided a limited number of working examples describing complex carbohydrate libraries that would not adequately instruct one of ordinary skill in the art to synthesize *every* complex carbohydrate library. Furthermore, applicant has not provided any examples of complex carbohydrate libraries with

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unnatural sugars, which may not be good substrates for the enzymes disclosed by applicant.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The quantity of experimentation needed to make or use the

claimed invention would be great. The art is inherently unpredictable (see above). The preparation of the complex carbohydrate libraries is unpredictable because there is no general glycosylation methodology for the preparation of linked saccharide units that proceeds quantitatively and stereospecifically. Furthermore, the list of enzymes provided by applicant would not provide for a means to synthesize *all* complex carbohydrates.

Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. (See *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991)). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicants regards as his invention.

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12. Claims 30-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. For **claim 30**, the term “complex carbohydrate” is a relative term, which renders the claim indefinite. The term “complex carbohydrate” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, the applicants have not disclosed the number of monomers, the amount of branching, or the type of linkages that would be required for an oligomer to be classified as a “complex carbohydrate.”

Furthermore, the specification does not provide a standard for ascertaining these limitations because according to Figures 2 and 3, a complex carbohydrate may contain any number of monomers and any number of branch points (there are entries in the CarbBank database showing single monomer complex carbohydrates with no branch points). Therefore, it is not possible to determine the metes and bounds of the invention as claimed. Consequently, claim 30 and all dependent claims i.e., 31-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. For **claim 34**, the term “harmless” in the phrase “under conditions that are harmless to carbohydrates” is indefinite and/or unclear. The term “harmless” is not defined by the claim and/or the specification, and one of ordinary skill in the art would not be reasonably apprised of

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the scope of the invention. For example, the term harmless denoted an impairment of the usefulness and/or value of the object i.e., the complex carbohydrates. However, it is not clear, which physical and/or chemical transformations would reduce the usefulness and/or value of the complex carbohydrates because the usefulness and/or value of an object is subjective i.e., in the eye of the beholder. Therefore, it is not possible to determine the metes and bounds of the invention as claimed. Consequently, claim 34 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. For **claims 52-53 and 57**, the term “representation” is not defined by the claim or the specification and is indefinite and/or unclear. For example, the term “representation” describes an embodiment of a specified quality, but the applicant has not specified what quality the “representation” portrays. Furthermore, applicant has not specified how the representation portrays the specified quality i.e., does it have to be an exact match or can the representation portray only 50% of the specified quality. Consequently, it is not possible to determine the metes and bounds of the invention as claimed. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

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to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 30-34, 36-40, 44-51 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dower et al (US #5,770,358) (Date of Patent is **June 23, 1998**; Date of filing is **September 16, 1992**), in further view of Nicolaou et al (Nicolaou, K. C.; Watanabe, N.; Li, J.; Pastor, J.; Winssinger, N. "Solid-Phase Synthesis of Oligosaccharides: Construction of a Dodecasaccharide" *Angew. Chem. Int. Ed.*, **1998**, 37(11), 1559-1561), and in further view of Schuster et al (Schuster, M.; Wang, P.; Paulson, J. C.; Wong, C. H. "Solid-Phase Chemical-Enzymatic Synthesis of Glycopeptides and Oligosaccharides" *J. Am. Chem. Soc.*, **1994**, 116, 1135-1136).

For **claim 30**, Dower et al teaches "methods for synthesizing random oligomers [including complex carbohydrates], with particular emphasis on particle-based synthesis methods [i.e., solid-phase library]" (see Dower et al, column 1, lines 11-18), which reads

on the preamble of claim 30 wherein a method of “producing an addressable combinatorial complex carbohydrate library” is disclosed. Furthermore, Dower et al teaches “random oligomers [that] are synthesized on solid support” and an “identifier tag”, which may be “attached directly to the oligomer with or without an accompanying particle, to a linker attached to the oligomer, to the solid support upon which the oligomer is synthesized, etc.” (see Dower et al, column 3, lines 14-15, and 21; see also column 3, lines 28-38; see also Glossary, column 6, paragraph 3, lines 30-31), which reads on the preamble and part (a) of claim 30 wherein the complex carbohydrate library is “addressable” having a “plurality of locations.” Dower also teaches that the carbohydrate libraries can be synthesized on a solid-support as mentioned above (see Dower et al, column 3, line 15), which also reads on part (a) of claim 30. Dower also teaches that the carbohydrate libraries can be synthesized with enzymes (see Dower et al, column 1, line 17; and see also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are “formed from the ... enzymatic addition of monomer subunits. Such oligomers include ... linear, cyclic, and branched polymers of ... polysaccharides”) (emphasis added), which reads on part (b) of claim 30.

Although Dower et al teaches every limitation of claim 30 (see above), Dower et al does not provide a specific example of a “complex carbohydrate library.” Furthermore, Dower et al does not provide a specific example of an “enzyme” used to make the complex carbohydrate library.

Nicolaou et al teaches a specific example of a “complex” carbohydrate library containing branched dodecasaccharides (see Nicolaou et al, page 1560, figure 2)

(showing the solid-phase synthesis of a branched dodecasaccharide), which reads on the preamble of claim 30 for producing a “complex” carbohydrate library. Furthermore, Schuster et al teaches a specific example of an enzyme used to link carbohydrates to a solid support (see Schuster et al, page 1136, scheme 1, reaction steps d-f).

For **claim 31**, Dower et al teaches that “the solid supports may be joined to the oligomers ... by means of one or more linker molecules” (see Dower et al, column 3, lines 38-30) (see also Dower et al, column 8, second to last paragraph) (“When bound to a solid support, the oligomer is usually attached by means of a linker”).

For **claim 32**, Dower et al does not provide a specific example of a linker that includes at least two contiguous bonds for a complex oligosaccharide library. However, Nicolaou teaches a linker with two contiguous covalent bonds (see Nicolaou et al, page 1559, figure 1).

For **claim 33**, Dower et al teaches that “one can cleave the linker from the bead, producing tagged oligomer in solution” (see Dower et al, column 23, lines 11-12) (see also Dower et al, column 8, second to last paragraph).

For **claim 34**, Dower et al teaches that “one can cleave the linker from the bead, producing tagged oligomer in solution” (see Dower et al, column 23, lines 11-12) (see also Dower et al, column 8, second to last paragraph), which reads on claim 34 wherein “the linker is cleavable under conditions that are harmless to carbohydrates” because Dower et al shows that tagged oligomers can be produced in solution. Furthermore, Nicolaou also teaches the cleavage of a linker under conditions that are harmless to

carbohydrates i.e., Nicolaou uses a light cleavable linker (see Nicolaou et al, page 1560, scheme 2, last step).

For **claim 36**, Dower et al does not provide a specific example of a linker for a complex oligosaccharide library. However, Nicolaou teaches a photolabile linker containing an alkyl chain (i.e., methylene group) (see Nicolaou et al, page 1559, figure 1).

For **claim 37**, Dower et al does not provide a specific example of a linker for a complex oligosaccharide library that is at least 20 Angstroms long. However, Schuster teaches a linker with 6 glycine residues that is >20 Angstroms long (see Schuster et al, page 1136, scheme 1, compound 3a showing NH-(Gly₆)-NH linker).

For **claim 38**, Dower et al teaches “one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPSTM chip.” (see Dower et al, columns 2-3, lines 64-67), which reads on claim 38 wherein “said solid support is ... a flat platform” since a VLSIPSTM chip is a flat platform.

For **claim 39**, Dower et al teaches “one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPSTM chip.” (see Dower et al, columns 2-3, lines 64-67).

For **claim 40**, Dower et al teaches “one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPSTM chip.” (see Dower et al, columns 2-3, lines 64-67), which reads on claim 40 wherein “said flat platform is ... a chip” because VLSIPSTM chips can have a “plurality of locations” spaced at any distance. “When the PTO shows a sound basis for believing that the products of

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the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 44**, Dower et al teaches that “glass” beads can be used as a solid support. (see Dower et al, columns 23, lines 62-67), which reads on claim 44 wherein “said solid support is ... glass.”

For **claim 45**, Dower et al does not provide a specific example of an oligosaccharide with at least two contiguous saccharide units. However, Schuster et al teaches a branched tetrasaccharide with two contiguous saccharide units (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 46**, Dower et al does not provide a specific example of a branched oligosaccharide. However, Schuster et al teaches a branched tetrasaccharide (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 47**, Dower et al does not provide a specific example of an oligosaccharide wherein “at least one of said plurality of said at least one branch is formed of identical core and branching saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide with identical core and branching units (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 48**, Dower et al does not provide a specific example of an oligosaccharide with at least four saccharide units. However, Schuster et al teaches a branched tetrasaccharide (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 49**, Dower et al does not provide a specific example of an oligosaccharide with at least five saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 50**, Dower et al does not provide a specific example of an oligosaccharide with at least six saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 51**, Dower et al does not provide a specific example of an oligosaccharide with at least seven saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 53**, Dower et al teaches the formation of “natural” carbohydrate libraries for screening (see Dower et al, column 1, line 17; and see also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are “formed from the ... enzymatic addition of monomer subunits. Such oligomers include ... linear, cyclic, and branched polymers of ... polysaccharides”).

For **claim 54**, Dower et al teaches that the complex combinatorial libraries may be “useful in therapeutic treatments such as for autoimmune diseases” (see Dower et al, column 7, lines 57), which reads on claim 54 wherein “said natural complex carbohydrates are associated with ... autoimmune disease.”

For **claim 55**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the “natural ligand” to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8).

For **claim 56**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the “natural ligand” to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8), which reads on claim 56 wherein “said human source is selected from the group consisting of a tissue, cells and body fluids” because antibodies and their corresponding antigens are found in tissue, cells and body fluids. “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 57**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the “natural ligands” to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 6, line 8).

For **claim 58**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the “natural ligand” to which the receptor binds and the

receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to build complex carbohydrate libraries as taught by Nicolaou et al with enzymes as taught by Schuster et al to screen for complex carbohydrate binding entities as taught by Dower et al because Dower et al explicitly states that “enzymes” can be used to synthesize carbohydrate libraries for screening and that these carbohydrate libraries can be “complex” (see Dower et al, column 1, line 17; and see also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are “formed from the ... enzymatic addition of monomer subunits. Such oligomers include ... linear, cyclic, and branched polymers of ... polysaccharides”) (emphasis added).

Furthermore, one of ordinary skill in the art would have been motivated to use the invention of Dower et al in a manner as taught by Nicolaou et al and Schuster et al because a larger variety of complex carbohydrates with potentially stronger binding affinity can be screened (see Nicolaou et al, page 1559, first paragraph) (emphasizing the need for “large and diverse libraries of oligosaccharides”). In addition, an elaborate array of protecting/deprotecting groups is not required for enzymatic synthesis. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Nicolaou shows that libraries with large complex carbohydrates can be made and Schuster et al shows that you can link carbohydrate monomers attached to polymers using enzymes.

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19. Claims 30-38, 44-51 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liang et al (Liang R.; Lin, Y.; Loebach, J.; Ge, M.; Uozumi, Y.; Klara, S.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. "Parallel Synthesis and Screening of a Solid Phase Carbohydrate Library" *Science*, **1996**, 274, 1520-1522), in further view of Seitz et al (Seitz, O.; Wong, C. H. "Chemoenzymatic Solution- and Solid-Phase Synthesis of O-Glycopeptides of the Mucin Domain of MAdCAM-1. A general Route to O-LacNAc, O-Sialyl-LacNAc, and O-Sialyl-Lewis-X Peptides" *J. Am. Chem. Soc.*, **1997**, 119, 8766-8776), and in further view of Seifert et al (Seifert, J. and Unverzagt, C. "Synthesis of three Biantennary N-Glycans containing the α -1,6 Core-Fucosyl Motif" *Tetrahedron Letters*, **1997**, 38(45), 7857-7860).

For *claim 30*, Liang et al teaches a method for the parallel synthesis and screening of a solid phase carbohydrate library (see Liang et al, title and abstract), which reads on the preamble of claim 30 wherein a method of "identifying a complex carbohydrate capable of binding an entity" is disclosed. Furthermore, Liang et al teaches a library containing "approximately 1300 di- and trisaccharides with chemical encoding on TentaGel resin so that each bead contained a single carbohydrate" (see Liang et al, abstract), which reads on part (a) of claim 30 to the extent that a trisaccharide is considered a "complex carbohydrate" because an addressable library of 1300 di- and trisaccharides is shown. In addition, Liang et al also teaches synthesizing the carbohydrate library on a "TentaGel resin so that each bead contained a single carbohydrate" (see Liang et al, abstract), which reads on part (a) (i) of claim 30 wherein a

“solid support having a plurality of locations” is provided i.e., the solid support is the TentaGel resin and the plurality of locations are the locations of the separate beads. Furthermore, Liang et al teaches a “strategy [that] can be used to identify carbohydrate-based ligands for any receptor ... [wherein] the screen may prove especially valuable for discovering new compounds that bind to proteins” (see Liang et al, abstract), which reads on part (b) of claim 30 wherein “screening said addressable combinatorial complex carbohydrate library with the entity for identifying the complex carbohydrate capable of binding the entity” i.e., the entity that is binding to the library in this case could include “any receptor” including “proteins.”

However, Liang et al does not teach the use of an “enzyme” to synthesize members of a complex carbohydrate library. Furthermore, Liang et al does not teach a carbohydrate library with members that are larger than 3 monomers and therefore “may” not teach “complex” carbohydrates. However, applicant shows in the specification (figure 3) that ~18% of the “complex carbohydrates” in the CarbBank database possess “only” 3 sugar residues, which implies that Liang does teach “complex” carbohydrates and, as a result, would not require the teachings of Seitz et al and Seifert et al as shown below.

In the alternative that the phrase “complex carbohydrates” denotes oligosaccharide members that are greater than 3 sugar residues, Seitz et al teaches that specific “enzymes” can be used to make large branched “complex” oligosaccharides on a solid support (see Seitz et al, page 8771, schemes 8-10 and especially scheme 12 on page 8772, reactions c-f) (showing the use of a “GalTase”, “SialTase” and “FucTase” to

synthesize a branched tetrasaccharide on a “CPG” solid support via peptide-HYCRON linker. Furthermore, Seifert et al teaches that enzymes can “extend” the length of a polymer bound oligosaccharide to create larger and more complex library members (see also Seifert et al, figure 1) (showing that enzymes can be used to “extend” the size of a complex oligosaccharide), which reads on part (a) (ii) of claim 30 wherein the “complex” addressable library is “enzymatically” synthesized.

For **claim 31**, Liang et al teaches that library members are attached to the TentaGel via a linker (see Liang et al, page 1520, figure 1, compound 1).

For **claim 32**, Liang et al teaches an S-Ph-CH₂C(O)NH linker (see Liang et al, page 1520, figure 1, compound 1).

For **claim 33**, Liang et al does not provide a specific example of a “cleavable” linker for a complex oligosaccharide library. However, Seitz teaches a cleavable linker (see Seitz et al, page 8772, scheme 12).

For **claim 34**, Liang et al does not provide a specific example of a “cleavable” linker for a complex oligosaccharide library. However, Seitz teaches a cleavable linker that does not “harm” the sugar residues (see Seitz et al, page 8772, scheme 12).

For **claim 35**, Liang et al teaches a linker that allows the attachment of a p-Nitrophenyl (see Liang et al, page 1520, figure 1, compound 2).

For **claim 36**, Liang et al teaches an S-Ph-CH₂C(O)NH linker (see Liang et al, page 1520, figure 1, compound 1), which reads on claim 36 wherein “said linker is ... an alkyl chain.” Furthermore, it should be noted that Seitz also teaches an “alkyl” linker (see Seitz et al, page 8768, scheme 2, showing HYCRON linker).

For **claim 37**, Liang et al does not provide a specific example of a linker for a complex oligosaccharide library that is at least 20 Angstroms long. However, Seitz teaches the HYCRON linker that is >20 Angstroms long (see Seitz et al, page 8768, scheme 2, showing HYCRON linker).

For **claim 38**, Liang et al teaches TentaGel beads (see Liang et al, page 1522, figure 4), which reads on claim 38 wherein "said solid support is ... addressable beads."

For **claim 44**, Liang et al teaches that Tentagel beads (see Liang et al, page 1522, figure 4), which reads on claim 44 wherein " said solid support is ... polyethylene glycol-polystyrene block copolymer."

For **claim 45**, Liang et al teaches a library of 1300 trisaccharides (see Liang et al, page 1520, abstract).

For **claim 46**, Liang et al does not provide a specific example of a branched oligosaccharide. However, Seitz et al teaches a branched tetrasaccharide (see Seitz et al, page 1136, schemes 10-12).

For **claim 47**, Liang et al does not provide a specific example of an oligosaccharide wherein "at least one of said plurality of said at least one branch is formed of identical core and branching saccharide units. However, Seitz et al teaches a branched tetrasaccharide with identical core and branching units (see Seitz et al, page 1136, scheme 10-12).

For **claim 48**, Liang et al does not provide a specific example of an oligosaccharide with at least four saccharide units. However, Seitz et al teaches a branched tetrasaccharide (see Seitz et al, page 1136, scheme 10-12).

For **claim 49**, Liang et al does not provide a specific example of an oligosaccharide with at least five saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 50**, Liang et al does not provide a specific example of an oligosaccharide with at least six saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 51**, Liang et al does not provide a specific example of an oligosaccharide with at least seven saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 53**, Liang et al teaches the formation of “natural” carbohydrate libraries for screening (see Liang et al, page 1521, figure 2).

For **claim 54**, Liang et al teaches that the complex combinatorial libraries may “provide an effective means of preventing or treating various diseases” including “tumorigenesis” (see Liang et al, page 1520, first paragraph), which reads on claim 54 wherein “said natural complex carbohydrates are associated with ... tumorigenesis.”

For **claim 55**, Liang et al does not provide a specific example of an oligosaccharide wherein “said natural complex carbohydrates are derived from a human source.” However, Seitz et al teaches “glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide” (see Seitz et al, page 1136, scheme 10-12).

For **claim 56**, Liang et al does not provide a specific example of an oligosaccharide wherein “said natural complex carbohydrates are derived from a human source.” However, Seitz et al teaches “glycopeptides containing an O-linked sialyl-

Lewis-X (Sle^x) tetrasaccharide” (see Seitz et al, page 1136, scheme 10-12), which reads on claim 56 wherein “said human source is selected from the group consisting of ... cells” because adhesion molecules that express Sle^x are found on the surface of cells.

For **claim 57**, Liang et al does not provide a specific example of an oligosaccharide wherein “said plurality of complex carbohydrate structures are a representation of domains of at least one natural complex carbohydrate.” However, Seitz et al teaches “glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide” (see Seitz et al, page 1136, scheme 10-12).

For **claim 58**, Liang et al does not provide a specific example of an oligosaccharide wherein “said at least one natural complex carbohydrate is derived from a human source.” However, Seitz et al teaches “glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide” (see Seitz et al, page 1136, scheme 10-12).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to build complex carbohydrate libraries with branched dodecasaccharides as taught by Seitz et al and Seifert et al using enzymatic synthesis to “identify carbohydrate-based ligands” as taught by Liang et al because Seitz et al specifically states that “Glycosyltransferases [i.e., enzymes] have shown to be versatile tools in oligosaccharide [solid-phase] synthesis” (see Seitz et al, page 8767, column 1, first paragraph; see also scheme 12) (showing that enzymes can be used in solid-phase synthesis, which is required for library production using resins). Furthermore, one of ordinary skill in the art would have been motivated to use the invention of Liang et al in a manner as taught by Seitz et al and Seifert et al because “a solid phase carbohydrate

library [requires] the ability to make a wide range of different glycosidic linkages both stereospecifically and in high yield” (see Liang et al, page 1520 column 3, first paragraph) and enzymes can solve this problem (see Seifert et al, Figure 3) (showing high yielding stereospecific monomer additions). In addition, enzymes do not require an elaborate array of different protecting groups, which are necessary in non-enzymatic oligosaccharide synthesis. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Seitz et al and Seifert et al teach that large complex oligosaccharides can be synthesized on solid-support using enzymes for “combinatorial access to complex structures” (see Seitz et al, page 8766, column 2, second paragraph).

Status of Claims/Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 8:30 a.m. to 4:30 p.m.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Joseph McKane can be reached on (703) 308-4537. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

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23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
August 7, 2002


PADMASHRI PONNALURI
PRIMARY EXAMINER